ELSEVIER

PII: S0032-3861(97)00400-X

Polymer Vol. 39 No. 3, pp. 743–745, 1998

0032-3861/97/$17.00+0.00

polymer communications

Gelation of fluoroalkylated 2-acrylamido-2-methylpropanesulfonic acid oligomers as potential for prevention of HIV-1 transmission

Hideo Sawada[a,b,*], Shinsuke Katayama[b], Yutaka Nakamura[a], Tokuzo Kawase[c], Yoshio Hayakawa[d] and Masanori Baba[e]

[a]*Department of Chemistry, Nara National College of Technology, Yata, Yamatokoriyama, Nara 639-11 Japan*
[b]*Department of Chemistry, Faculty of Advanced Engineering, Nara National College of Technology, Yamatokoriyama, Nara 639-11, Japan*
[c]*Faculty of Human Life Science, Osaka City University, Sugimoto, Sumiyoshi-ku, Osaka 558, Japan*
[d]*National Industrial Research Institute of Nagoya, Kita-ku, Nagoya 462, Japan*
[e]*Division of Human Retroviruses, Center for Chronic Viral Diseases, Faculty of Medicine, Kagoshima University, Sakuragaoka, Kogoshima 890, Japan*
(Received 26 December 1996; revised 22 April 1997)

End-capped fluoroalkyl segments in 2-acrylamido-2-methylpropanesulfonic acid oligomers could serve as a new interaction for gelation in both water and organic polar solvents under non-cross-linked conditions, and these gelling oligomers were found to be selective inhibitors of human immunodeficiency virus type 1 (HIV-1) replication, suggesting that the compounds have the potential to prevent HIV-1 transmission through their chemical and biological properties. © 1997 Published by Elsevier Science Ltd.

(Keywords: gelation; fluoroalkylated oligomers; anti-HIV-1 activity)

Introduction

Recently, there has been great interest in organofluorinated materials, especially longer fluoroalkyl segment containing materials. These exhibit various unique properties such as excellent chemical and thermal stability, low surface energy, and a low refractive index and dielectric constant, which cannot be achieved by the corresponding non-fluorinated materials[1,2]. We have previously developed a series of novel oligomers containing two fluoroalkyl end groups by the use of fluoroalkanoyl peroxides as intermediates, and have also shown that these fluoroalkylated oligomers exhibit unique properties imparted by fluorine, although the compounds are oligomeric (high molecular mass) materials[3–10]. In the course of this study, we obtained the surprising finding that 2-acrylamido-2-methylpropanesulfonic acid oligomers containing fluoroalkyl end groups cause gelation not only in water but also in organic polar solvents such as methanol, ethanol, *N,N*-dimethylformamide and dimethyl sulfoxide. Hitherto, it was widely accepted that the driving factors for thermo-irreversible (chemical) and thermo-reversible (physical) gelation are covalent bonds which build up a chemically cross-linked gel, and intermolecular hydrogen bonding or ionic interactions, respectively[11]. Some macromolecules are known to cause chemical and physical gelation in aqueous solutions, but the application of these materials to organogels has hitherto been limited. To the best of our knowledge, however, our finding is the first example of the strong interaction between fluoroalkyl segments for both hydro- and organo-gelation being involved in establishing the gel network. Furthermore, we discovered that these fluoroalkylated gelling oligomers are applicable to novel gelling materials possessing selective anti-human immunodeficiency virus type 1 (HIV-1) inhibition properties in vitro.

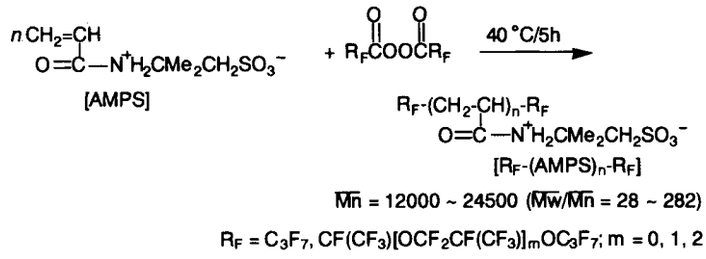
A series of fluoroalkylated 2-acrylamido-2-methylpropanesulfonic acid oligomers (R_F–(AMPS)$_n$–R_F) were prepared by the reactions of fluoroalkanoyl peroxides and 2-acrylamido-2-methylpropanesulfonic acid (AMPS) as shown in *Scheme 1*.

Similarly, we succeeded in preparing a series of fluoroalkylated AMPS co-oligomers by using comonomers such as trimethylvinylsilane and methyl methacrylate, as shown in *Scheme 2*.

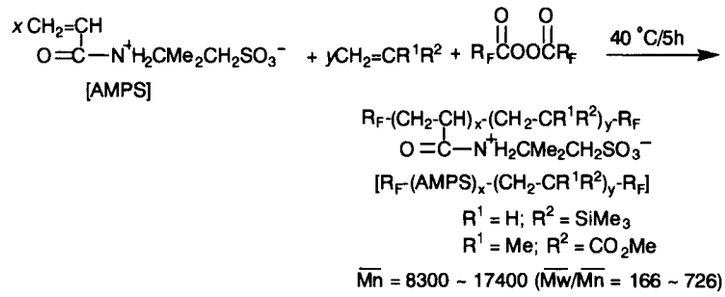
The corresponding non-fluorinated AMPS oligomer (–(AMPS)$_n$–; $\overline{M_n} = 5400$ ($\overline{M_w}/\overline{M_n} = 3.35$)) was prepared by using 2,2′-azobis(2-methylpropionamidine) dihydrochloride. The oligomers obtained were identified by i.r., and ^{1}H and ^{19}F n.m.r. spectroscopy. (Selected spectroscopic data for the oligomers R_F–(AMPS)$_n$–R_F, where R_F is $CF(CF_3)OCF_2CF(CF_3)OC_3F_7$, are given as follows. I.r. (cm^{-1}): 3370 (NH_2,OH), 1647 (C=O), 1303 (CF_3), 1255 (SO_3^-), 1226 (CF_2) and 1101 (SO_3^-); ^1H n.m.r. (D_2O): δ 1.38–1.83 (CH_2), 1.53 (CH_3), 1.97–2.30 (CH), around 3.19–3.57 (CH_2); ^{19}F n.m.r. (D_2O, ext CF_3CO_2H): δ – 4.42 to – 8.42 (26F), – 54.0 to – 56.26 (6F), 66.78 (2F).)

Both perfluoropropylated and perfluorooxaalkylated oligomers were obtained in excellent to moderate yields (30–58%) under very mild conditions. The molecular weights of the obtained oligomers were measured by gel permeation chromatography (g.p.c.) (calibrated with standard poly(ethylene glycol) by using 0.5 mol dm^{-3} Na_2HPO_4 solution as the eluent), and the obtained molecular weights ($\overline{M_n}$) were relatively high (8300–24 500). Considering the fact that water-soluble fluoroalkylated oligomers easily form molecular aggregates in aqueous solutions, this finding suggests that the values obtained by g.p.c. indicate the apparent molecular weights. Interestingly, the $\overline{M_w}/\overline{M_n}$

* To whom correspondence should be addressed



Scheme 1



Scheme 2

values for these fluoroalkylated oligomers are extremely high (28–726) compared to the value for the corresponding non-fluorinated one ($\overline{M}_w/\overline{M}_n = 3.25$). This result also suggests that these fluoroalkylated oligomers form aggregates.

Our fluoroalkylated oligomers are easily soluble not only in water but also in polar organic solvents such as methanol, ethanol, *N,N*-dimethylformamide and dimethyl sulfoxide in dilute conditions (below about 0.5 g dm^{-3}). Surprisingly, at concentrations above 1.0 g dm^{-3}, all oligomer–solvent systems formed gels. To study this unique gelation, we measured the viscosity of aqueous solutions of these oligomers at 30°C. The results are shown in *Figure 1*.

As can be seen from *Figure 1*, the viscosities of $-(AMPS)_n-$, fluoroalkylated oligomers containing trimethylammonium segments ($R_F-(CH_2CHCO_2(CH_2)_2N^+Me_3Cl^-)_n-R_F$; $R_F = C_3F_7$) and sulfo segments ($R_F-(CH_2CMeCO_2(CH_2)_2SO_3H)_n-R_F$; $R_F = C_3F_7$) did not increase remarkably on increasing their concentration, although these fluoroalkylated oligomers were found to form molecular aggregates like micelles in aqueous solutions[12,13]. On the other hand, the viscosities of our fluoroalkylated AMPS oligomers increased dramatically with increasing concentration, and it became impossible to measure their viscosities owing to gelation at concentrations above 0.5 or 1.0 g dm^{-3}. We also tried to measure the temperature at which the gel melts; however, the gel did not melt both in water and in organic solvents even when it was heated from 30°C to around 95°C. Therefore, it has been reasonably concluded that our fluoroalkylated AMPS oligomers can form a physical gel with water, methanol, ethanol, *N,N*-dimethylformamide and dimethyl sulfoxide. In addition, it may be suggested that the fluoroalkyl segments are strongly connected with the establishment of the gel network.

The gelling ability of some fluoroalkylated AMPS oligomers were also studied by measuring minimum concentrations of these oligomers necessary for gelation according to the method reported by Hanabusa *et al.*[14,15]. The minimum concentrations for gelation in water and dimethyl sulfoxide (DMSO) at 30°C were as follows.

R_F	Minimum gel concentration, gelator/medium (g dm^{-3})	
	Water	DMSO
In $R_F-(AMPS)_n-R_F$		
C_3F_7	25	13
$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	31	11
$CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	33	21
In $R_F-(AMPS)_x-(CH_2CHSiMe_3)_y-R_F$		
C_3F_7	6	6
$CF(CF_3)OC_3F_7$	6	8
$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	7	9
In $R_F-(AMPS)_x-(CH_2CMeCO_2Me)_y-R_F$		
C_3F_7	2	5
$CF(CF_3)OC_3F_7$	9	7
$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	5	5

The gelling ability of fluoroalkylated co-oligomers is fairly superior to that of homo-oligomers, taking into account that the minimum gel concentrations are 2–9 g dm^{-3} for co-oligomers and 11–33 g dm^{-3} for homo-oligomers. This result is in fair agreement with the values of $\overline{M}_w/\overline{M}_n$ for oligomers shown in *Scheme 1Scheme 2*, and the oligomers possessing higher $\overline{M}_w/\overline{M}_n$ values (more polydispersant) were found to exhibit higher gelling ability. These findings would depend upon the co-oligomers being likely to promote gelation sterically compared to the corresponding homo-oligomers. These fluoroalkylated oligomers also exhibited a quite similar property to that of common water-swollen cross-linked polymeric hydrogels, i.e. the fluoroalkylated AMPS oligomers in water exhibited extremely large water adsorption abilities. For example, the amount of water alone adsorbed by the fluororalkylated gelling co-oligomer $R_F-(AMPS)_x-CH_2CHSiMe_3)_y-R_F$ ($R_F = C_3F_7$) led to an attained weight 213 times the original weight of the dry gel.

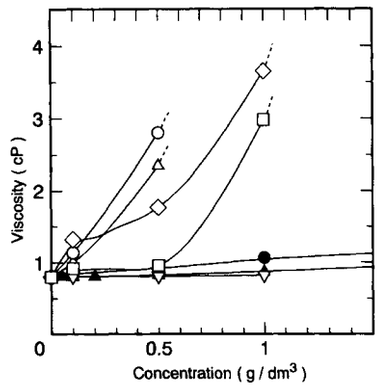


Figure 1 Effect of concentration on viscosity measured at 30°C by using a falling-sphere viscometer

R_F-(AMPS)$_n$-R_F

○ : R_F=C_3F_7- ($\overline{Mn}$=24500)

△ : R_F=$C_3F_7OCF(CF_3)$- ($\overline{Mn}$=20500)

□ : R_F=$C_3F_7OCF(CF_3)CF_2OCF(CF_3)$- ($\overline{Mn}$=12000)

◇ : R_F=$C_3F_7OCF(CF_3)CF_2OCF(CF_3)CF_2OCF(CF_3)$- ($\overline{Mn}$=24000)

▽ : -(AMPS)$_n$- ($\overline{Mn}$=5400)

● : C_3F_7-(CH$_2$-CH)$_n$-C_3F_7 with $CO_2(CH_2)_2N^+Me_3Cl^-$ ($\overline{Mn}$=77000)

▲ : C_3F_7-(CH$_2$-CMe)$_n$-C_3F_7 with $CO_2(CH_2)_2SO_3H$ ($\overline{Mn}$=21500)

A striking characteristic of our AMPS oligomers is the ability to form gels not only in water but also in organic polar solvents. This feature is attributable to the fluoralkyl segments being solvophobic in aqueous and organic media, and enhancing aggregation due to the strong interaction between the fluoroalkyl segments. From such a point of view, the reason why our AMPS oligomers can form a gel in both water and organic media would be the occurrence of synergistic interactions, one being the aggregation of fluoroalkyl units, and the other being ionic interactions of the amide cations and the sulfonate anions as shown schematically in *Figure 2*.

On the other hand, in the case of the corresponding non-fluorinated oligomer –(AMPS)$_n$–, only ionic interactions would operate and gelation would not occur.

Moreover, not only an ionic interaction but also a hydrogen-bonding interaction could be expected to participate in the gelator which is constructed by the aggregation of fluoralkyl units. In fact, R_F–[$CH_2CHCONHC(CH_2OH_3)$]$_n$–R_F compounds (where R_F is a fluoroalkyl group) were found to cause similar physical gelation in both water and in organic polar solvents such as DMSO.

In this way, it was demonstrated that the aggregation of fluoralkyl segments in water and/or in organic media becomes a new driving factor for gelation, as well as such well-known interactions as the hydrogen bond and ionic interactions.

More interestingly, fluoralkylated gelators have been found to inhibit HIV-1 replication in cell structures. The 50% effective concentrations of the oligomers were 0.23–2.3 $\mu g\ ml^{-1}$. These values are superior to those for dextran sulfate, a potent and selective inhibitor of HIV-1 replication[16]. On the other hand, the non-fluorinated oligomers were toxic to the host cells. The mechanism of the action of gelling oligomers may also be attributed to the inhibition of

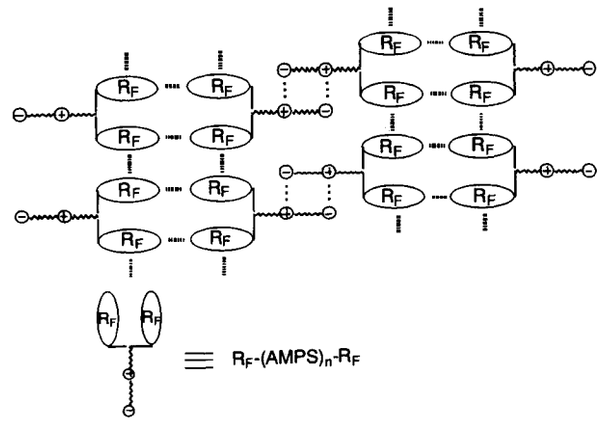


Figure 2 Schematic illustration of the gelation of R_F–(AMPS)$_n$–R_F

virus adsorption, as was previously demonstrated for fluoroalkylated acrylic acid oligomers[17–19]. Therefore, the compounds may have the potential to prevent HIV-1 transmission through their unique properties, such as gelation and anti-viral activity.

Acknowledgements

This work was partially supported by Grant-in-Aids for Scientific Research no. 07641042 and 09650945 from the Ministry of Education, Science and Culture, Japan, for which the authors are grateful.

References

1. Eds R. E. Banks, B. E. Smart and J. C. Tatlow, *Organofluorine Chemistry*, Plenum, New York, 1994.
2. Eds J. F. Liebman, A. Greenberg and W. R. Dolbier Jr., *Fluorine-Containing Molecules*, VCH, Weinheim, 1988.
3. Sawada, H., *Chem. Rev.*, 1996, **96**, 1779.
4. Sawada, H. and Nakayama, N., *J. Chem. Soc. Chem. Commun.*, 1991, 677.
5. Sawada, H., Gong, Y.F., Minoshima, Y., Matsumoto, T., Nakayama, M., Kosugi, M. and Migita, T., *J. Chem. Soc. Chem. Commun.*, 1992, 537.
6. Sawada, H., Minoshima, Y. and Nakajima, H., *J. Fluorine Chem.*, 1992, **65**, 169.
7. Sawada, H., Yamaguchi, K., Mitani, M., Nakajima, H., Nishida, M. and Moriya, Y., *Polymer*, 1994, **35**, 444.
8. Sawada, H., Tanba, K., Oue, M., Kawade, T., Mitani, M., Minoshima, Y., Nakajima, H., Nishida, M. and Moriya, Y., *Polymer*, 1994, **35**, 4028.
9. Sawada, H., Itoh, N., Kawase, T., Mitani, M., Nakajima, H., Nishida, M. and Moriya, Y., *Langmuir*, 1994, **10**, 994.
10. Sawada, H., Tanba, K., Oue, M., Kawase, T., Hayakawa, Y., Mitani, M., Minoshima, Y., Nishida, M. and Moriya, Y., *Polymer*, 1995, **36**, 2103.
11. Guenet, J.M., *Thermoreversible Gelation of Polymers and Biopolymers*, Academic Press, 1992.
12. Sawada, H., Katayama, S., Oue, M., Kawase, T., Hayakawa, Y., Baba, M., Tomita, T. and Mitani, M., *J. Jpn. Oil Chem. Soc.*, 1996, **45**, 161.
13. Sawada, H., Ohashi, A., Baba, M., Kawase, T. and Hayakawa, Y., *J. Fluorine Chem.*, 1996, **79**, 149.
14. Hansabusa, K., Watanabe, Y., Kimura, M., Koyama, T. and Shirai, H., *Seni Gakkaishi*, 1996, **52**, 129.
15. Hanabusa, K., Naka, Y., Koyama, T. and Shirai, H., *J. Chem. Soc., Chem. Commun.*, 1994, 2683.
16. Baba, M., Pauwels, R., Balzarini, J., Arnout, J., Desmyter, J. and DeClercq, E., *Proc. Natl. Acad. Sci. USA*, 1988, **85**, 6132.
17. Baba, M., Kira, T., Shigeta, S., Matsumoto, T. and Sawada, H., *J. Aquired Immun. Defic. Syndr.*, 1994, **7**, 24.
18. Sawada, H., Tanba, K., Itoh, N., Hosoi, C., Oue, M., Baba, M., Kawase, T., Mitani, M. and Nakajima, H., *J. Fluorine Chem.*, 1996, **77**, 51.
19. Sawada, H., Ohashi, A., Oue, M., Baba, M., Abe, M., Mitani, M. and Nakajima, H., *J. Fluorine Chem.*, 1995, **75**, 121.